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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,123	MARTIN ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5,7,11,12,14,17-21,23-27 and 34-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,7,11,12,14,17-21,23-27 and 34-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/6/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/6/08 has been entered.

Claims 2-5, 7, 11, 12, 14, 17-21, 23-27 and 34-39 are currently pending.

Claim Rejections - 35 USC § 112-Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 2-5, 7, 11, 12, 14, 17-21, 23-27 and 34-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to pharmaceutical compositions comprising isolated polypeptides comprising amino acid sequences which are from at least 90-95% identical to SEQ ID No: 2 with the function of inducing an immune response against

N.meningitidis. Fragments comprising at least 10 amino acids which induce an immune response against a bacterium from ***any*** species of Neisseria in pharmaceutical compositions and as chimeric polypeptides are also claimed. Methods of using a variant polypeptide at least 90-95% identical to SEQ ID No: 2 or fragments of as little as 10 contiguous amino acids to **prevent** or treat N.meningitidis infection are also claimed. Fragments 68-80 and 108-125 are also exemplified in new claims 36-39.

First, the breadth of the instant claims is drawn to polypeptides which are not specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions.

The instant claims are drawn to proteins comprising a sequence with a given percent similarity to a protein. Selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of

decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the native protein on the bacteria, and be ineffective in treating or preventing diseases or conditions caused by infection with said bacteria. Applicants have provide no guidance to enable one of ordinary skill in the art how to determine, without undue experimentation, the effects of different amino acid substitutions and the nature and extent of the changes that can be made. It is expensive and time consuming to make amino acid substitutions at more than one position, in a particular region of the protein, in view of the many fold possibilities for change in structure and the uncertainty as to what utility will be possessed. See Mikayama et al. (Nov.1993. Proc.Natl.Acad.Sci. USA, vol. 90 : 10056-10060) which teaches that the three-dimensional structure of molecules is important for their biological function and even a dingle amino acid difference may account for markedly different biological activities. Rudinger et al. (June 1976. Peptide Hormones. Biol.Council. pages 5-7) also teaches that amino acids owe their 'significance' to their inclusion in a pattern which is directly involved in recognition by, and binding to, the receptor and the

significance of the particular amino acids and sequences for different amino acids cannot be predicted a priori, but must be determined from case to case by painstaking experimental study.

The specification is also not enabled for vaccines or methods of using the full-length proteins set forth in SEQ ID Nos: 2, variants of these polypeptides which are at least 90% identical to SEQ ID NO: 2 to protect or prevent against infection with N.meningitidis. The bacterial vaccine and treatment art is highly unpredictable. The instant specification provides no results of treating or protecting these diseases, particularly through the use of variant polypeptides. In such an unpredictable art, specific evidences would need to be present in order to enable such a scope of invention. Additionally, the specification fails to identify any 10-mer fragments which could prevent or provide protection against infection with N.menigitidis.

The specification is not enabled for use of variant polypeptide sequences or fragments claimed treatment methods or pharmaceuctical compostions. The location of protective epitopes has not been identified. Often times it takes more than one epitope to provide a protective effect. As stated above, selective point mutation to one key antigen could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection/function, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of function.

The instant specification provides no results of treating or protecting these diseases. In such an unpredictable art, specific evidences would need to be present in order to enable such a scope of invention. The specification does show some in vitro immunological assays using the full-length protein set forth in SEQ ID NO:2. None are provided for 10-mer fragments or variants from 90-95% identical SEQ ID NO: 2. These results do not enable in vivo methods and they do not enable use of fragments or variants from SEQ ID NO:2. When considering a bacterial antigen as a vaccine candidate, three major considerations must be raised (1) the antigen must be conserved among strains of the bacterial species whose disease one wishes to prevent; (2) it must generate protective antibody such that the antibody to the antigen prevents disease; and (3) it must be a good immunogen such that protective antibodies are elicited in the population at risk and that these antibodies persist for sufficient time to provide protection throughout the risk. Even when an antigen meets these three considerations, further testing often indicates that the antigen will not be effective as a vaccine. The instant specification has not demonstrated that the full-length protein, variants or any of its fragments meet these 3 considerations and do not show prevention or protection against N.meningitidis.

Given the lack of guidance contained in the specification, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Response to Applicant's Arguments:

Applicants argue that the specification, although not providing working examples, enables vaccines and treatment methods using variants from 90% identity to SEQ ID NO: 2 to **prevent** or treat a Neisserial infection caused by N.meningitidis. Prophetic examples and teachings are provided. It is noted that, Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." The standard for enabling protection and prevention is very high in the bacterial vaccine art. Challenge experiments are needed to demonstrate success. Additionally, the specification has not shown that any of the variants, full-length proteins or 10+-mer fragments could induce a protective immune response to ***or prevent*** *N.meningitidis* infection. The identification alone of a protein, variant or fragment which is 90% identical is not enough, the showing that this polypeptide would possess the functional ability to induce a protective immune response to ***or prevent*** *N.meningitidis* infection is required by the claims. Enablement and conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation. A mere statement that it is part of the invention and a reference to a potential method of isolating it is not sufficient. The functional polypeptide itself is required.

When considering a bacterial antigen as a vaccine candidate, three major considerations must be raised (1) the antigen must be conserved among strains of the bacterial species whose disease one wishes to prevent; (2) it must generate protective antibody such that the antibody to the antigen prevents disease; and (3) it must be a good immunogen such that protective antibodies are elicited in the population at risk and that these antibodies persist for sufficient time to provide protection throughout the risk. Even when an antigen meets these three considerations, further testing often indicates that the antigen will not be effective as a vaccine. The instant specification has not demonstrated that the full-length protein, variants or any of its fragments meet these 3 considerations and do not show prevention or protection against N.meningitidis.

Claim Rejections - 35 USC § 112-Written Description

4. Claims 2-4, 7, 12, 14, 17-21, 23-27 and 34-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID NO:2 and antigenic portions from this sequence. Therefore, the written description is not commensurate in scope with the claims which encompass variants of SEQ ID NO:2 with at least 90-95% homology to SEQ ID NO:2.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

With the exception of SEQ ID NO: 2, the skilled artisan cannot envision the detailed structure of the encompassed polypeptides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The polypeptide itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Reagents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a

nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Therefore, the full breadth of the claims does not meet the written description provisions of 35 USC 112, first paragraph.

Response to Applicant's Arguments:

Applicants argue that they teach the structure of SEQ ID NO: 2, full-length NspaA polypeptide and the nucleic acid sequence which encodes it, e.g., SEQ ID NO: 1. This has been fully and carefully considered but is not deemed persuasive. The recitation of "inducing an immune response against N.menigitidis" does not convey a common structure or specific function. The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and the claims do not provide any guidance on the structure of the polypeptide and what changes can or can not be made in order to achieve a naturally-occurring or artificially modified variant that have the same function, molecular weight and immunological properties. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics

that identify members of the genus, and because the genus is highly variant, the "same function", e.g., generic immunological properties, are insufficient to describe the genus of variant NspaA polypeptides and fragments of that function equivalently. One of skill in the art would reasonable conclude that the disclosure of a single SEQ ID NO, e.g, SEQ ID NO: 2 , fails to provide a representative number of naturally-occurring or artificially modified variant species of NspaA to describe the claimed polypeptide genera. Applicants were not in possession of the claimed genus because the specification does not convey to one of skill in the art a representative number of variants in structure ad function of any such polypeptide that has the claimed/structure and function. The genus of polypeptides with the claimed function is substantial and highly variant because the polypeptides do not have a common structure and specific function, e.g, the generic ""inducing an immune response against [any] Neisseria" is not a 'specified function. As such, generic polypeptide sequences that are unrelated via structure and function are highly variant and not conveyed by way of written description by the specification at the time of filing. As such the specification lacks written description for the highly variant genus of single function polypeptides and one skilled in the art would not recognize that applicants had possession of the genus of claimed polypeptides. Applicants have not provided a representative number of naturally occurring or modified-modified variants that possess the same function as NspaA. They provide prophetic teachings of acceptable variants and fragments, but have not identified a common core. There is inadequate written description to support claims to species homologues of the disclosed polypeptide.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 2-5, 7, 11, 12, 14, 17-21, 23-27 and 34-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brodeur et al (WO 96/29412) in view of anyone of Ward et al (Microbial Pathogenesis. 1996. 21: 499-512), Idanpaan-Heikkila et al (Vaccine. 1995. 13(16): 1501-8), or Wright et al (Infection and Immunity, August 2002, 70(8): 4028-4034).

Brodeur et al teach an isolated outer membrane protein from *Neisseria meningitidis* which is ***100% identical*** to the protein taught by Applicant's as SEQ ID NO: 2. Fragments of this protein are also taught as well as methods for producing it recombinantly. See top of page 6 and pages 18-19. It is taught that the protein may be used in prophylactic and diagnostic compositions and methods useful in the treatment, prevention and diagnosis of *Neisseria meningitidis*. See abstract. Hybrid or chimeric proteins are also taught. Brodeur et al teach that this protein is highly conserved.

However, Brodeur et al do not specifically teach the use of a liposome, particularly one comprising a bacterial phospholipid, with their polypeptide.

Ward et al teach that the incorporation of isolated *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to

an active conformation without the negative toxic effects associated with LPS. The use of adjuvants such as monophosporyl lipid A or muramyl dipeptide along with the liposomes is specifically taught. However, it is taught that an effective bactericidal response was obtained with the purest preparation of protein incorporated into liposomes. Page 503 teaches how to incorporate the proteins into liposomes. Liposomes composed of phosphatidylcholine and cholesterol are taught. Page 508 teaches that the advantage of using liposomes is primarily the potential for folding of the protein in the liposomal membrane to a native-like conformation and the inherent immunoadjuvant activity of the liposome vesicles.

Idanpaan-Heikkila et al teach that when the outer membrane protein P1 from *N.meningitidis* was reconstituted with of phosphatidylcholine into liposomes, native antigenic epitopes were formed. It is taught that the liposomes were reproducibly immunogenic at a low dose without any other adjuvant. The antibodies produced were both bactericidal and protective against infection in the infant rat model.

Wright et al teach the incorporation of the recombinant PorB outer membrane protein of N.meningitidis into liposomes for use as a vaccine. The liposome preparations proved to induce a much greater immune response than the PorB adsorbed to $Al(OH)_3$. It is further taught that reactivity with native protein was considerably enhanced by incorporation of the adjuvant monophosporyl lipid A into the liposome. See abstract.

It would have been prima facie obvious to incorporate the isolated *N.meningitidis* protein taught by Brodeur et al (which is the same as the protein taught by Applicant's

as SEQ ID NO:2) or its immunogenic fragments thereof, as well as fusion or chimerics of said protein, into liposomes because the prior art, as evidenced by Ward, Idanpaan-Heikkila et al, and Wright, extensively taught that incorporating isolated, denatured or recombinant *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to an active conformation without the negative toxic effects associated with LPS. One of ordinary skill in the art would have been motivated to incorporate the protein taught by Brodeur into liposomes because doing so not only allows for the protein to obtain native-like conformation, but also has the added benefit of the inherent immunoadjuvant activity of the liposome vesicles. The secondary references further teach that the liposomes may be used with or without a further adjuvant. The protein taught by Brodeur et al would inherently comprise an 'epitope-bearing portion'. The doses taught in instant claim 27 is consistent with what is taught by Brodeur et al. The prior art teaches the identical polypeptide and the idea that using liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation as well as contain an additional adjuvant activity. Although the prior art references do not specifically recite that the liposome may be of bacterial cell origin, it was well known in the prior art that pharmaceutical compositions comprising liposomes could be constituted from phospholipids from bacterial cells, soybean or eggs and any one of these sources would work equally as well as functional equivalents.

Response to Applicants' Arguments:

Applicants argue that Brodeur, nor the combination of reference, teach a NspaA protein, variant or fragment thereof formuated with a liposome comprising a bacterial phospholipid in a pharmaceutical composition. They argue that the prior art as a whole must suggest the desirability of making a the combination. This has been fully and carefully considered but is not deemed persuasive. First, the prior art as a whole does teach or suggest the desirability of formulating a Gram-negative bacterial protein with a liposome. The term 'pharmaceutical composition' is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the prior art references recited above, e.g., Ward, Idanpaan-Heikkila et al, and Wright, extensively teach that incorporating isolated, denatured or recombinant *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to

an active conformation without the negative toxic effects associated with LPS. One of ordinary skill in the art would have been motivated to incorporate the protein taught by Brodeur into liposomes because doing so not only allows for the protein to obtain native-like conformation, but also has the added benefit of the inherent immunoadjuvant activity of the liposome vesicles. The secondary references further teach that the liposomes may be used with or without a further adjuvant. Although the prior art references do not specifically recite that the liposome may be of bacterial cell origin, it was well known in the prior art that pharmaceutical compositions comprising liposomes could be constituted from phospholipids from bacterial cells, soybean or eggs and any one of these sources would work equally as well as obvious functional equivalents, absent evidence to the contrary.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references **individually** where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The prior art, taken as a whole, clearly provides motivation for combining/formulating a known Neisseria protein with a liposome of any origin, including one comprising a bacterial phospholipid.

It is noted that only instant claims 17 and 19 require the additional use of an adjuvant. The secondary references further teach that the liposomes may be used *with or without* a further adjuvant. . Wright et al specifically teach that reactivity with native

protein was considerably enhanced by incorporation of the adjuvant monophosporyl lipid A into the liposome.

7. Claims 1-5, 7, 11-27, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over any one of Cadieux et al (Infect. Immun. Sept. 1999. 67(9): 4955-4959), Plante et al (Infect. Immun. June 1999. 67(6): 2855-2861) or Martin et al (J.Exp.Med. 1997. 185(7): 1173-1183) in view of anyone of Ward et al (Microbial Pathogenesis. 1996. 21: 499-512), Idanpaan-Heikkila et al (Vaccine. 1995. 13(16): 1501-8), or Wright et al (Infection and Immunity, August 2002, 70(8): 4028-4034).

Cadieux et al, Martin et al and Plante et al teach an isolated surface protein from *Neisseria meningitidis* which is 100% identical to the protein taught by Applicant's as SEQ ID NO: 2. Fragments of this protein are also taught as well as methods for producing it recombinantly. The references teach that the protein is highly conserved and is capable of protecting against meningococcal infections.

However, Cadieux et al, Martin et al and Plante et al do not specifically teach the use of a liposome, particularly one comprising a bacterial phospholipid, with their polypeptide.

Ward et al teach that the incorporation of isolated *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to an active conformation without the negative toxic effects associated with LPS. The use of adjuvants such as monophosporyl lipid A or muramyl dipeptide along with the

liposomes is specifically taught. However, it is taught that an effective bactericidal response was obtained with the purest preparation of protein incorporated into liposomes. Page 503 teaches how to incorporate the proteins into liposomes. Liposomes composed of phosphatidylcholine and cholesterol are taught. Page 508 teaches that the advantage of using liposomes is primarily the potential for folding of the protein in the liposomal membrane to a native-like conformation and the inherent immunoadjuvant activity of the liposome vesicles.

Idanpaan-Heikkila et al teach that when the outer membrane protein P1 from *N.meningitidis* was reconstituted with of phosphatidylcholine into liposomes, native antigenic epitopes were formed. It is taught that the liposomes were reproducibly immunogenic at a low dose without any other adjuvant. The antibodies produced were both bactericidal and protective against infection in the infant rat model.

Wright et al teach the incorporation of the recombinant PorB outer membrane protein of N.meningitidis into liposomes for use as a vaccine. The liposome preparations proved to induce a much greater immune response than the PorB adsorbed to $Al(OH)_3$. It is further taught that reactivity with native protein was considerably enhanced by incorporation of the adjuvant monophosporyl lipid A into the liposome. See abstract.

It would have been prima facie obvious to incorporate the isolated *N.meningitidis* protein taught by any one of Cadieux et al, Martin et al or Plante et al (which is the same as the protein taught by Applicant's as SEQ ID NO:2), into liposomes because the prior art, as evidenced by Ward, Idanpaan-Heikkila et al, and Wright, extensively taught

that incorporating isolated, denatured or recombinant *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to an active conformation without the negative toxic effects associated with LPS. One of ordinary skill in the art would have been motivated to incorporate the protein taught by Cadieux et al, Martin et al and Plante et al into liposomes because doing so not only allows for the protein to obtain native-like conformation, but also has the added benefit of the inherent immunoadjuvant activity of the liposome vesicles. The secondary references further teach that the liposomes may be used with or without a further adjuvant. The protein taught by Cadieux et al, Martin et al and Plante et al would inherently comprise an 'epitope-bearing portion'. The doses taught in instant claim 27 is consistent with what is taught by Brodeur et al. Although the prior art references do not specifically recite that the liposome may be of bacterial cell origin, it was well known in the prior art that pharmaceutical compositions comprising liposomes could be constituted from phospholipids from bacterial cells, soybean or eggs and any one of these sources would work equally as well as obvious functional equivalents. It is noted that the instant disclosure allows for the liposome to be synthesized or extracted from bacterial cells, soybeans or eggs. Phosphatidyl choline, phosphatiddylserine, phosphatidylgycerol, glycerides, steroids, e.g., cholesterol are all suggested.

The protein claimed and fragments thereof was very well known at the time the invention was made. Additionally, it was very well known that extensively teach that

incorporating isolated, denatured or recombinant *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to an active conformation without the negative toxic effects associated with LPS. One of ordinary skill in the art would have been motivated to incorporate the known NSA protein taught by Brodeur into liposomes, including those comprising a bacterial phospholipid, because doing so not only allows for the protein to obtain native-like conformation, but also has the added benefit of the inherent immunoadjuvant activity of the liposome vesicles.

Response to Applicants' Arguments:

Applicants argue that Plante, nor the combination of reference, teach a NspaA protein, variant or fragment thereof formuated with a liposome in a pharmaceutical composition. They argue that the prior art as a whole must suggest the desirability of making a the combination. This has been fully and carefully considered but is not deemed persuasive. First, the prior art as a whole does teach or suggest the desirability of formulating a Gram-negative bacterial protein with a liposome, synthetic or natural source. The term 'pharmaceutical composition' is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In response to applicant's

argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the prior art references recited above, e.g., Ward, Idanpaan-Heikkila et al, and Wright, extensively teach that incorporating isolated, denatured or recombinant *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to an active conformation without the negative toxic effects associated with LPS. One of ordinary skill in the art would have been motivated to incorporate the protein taught by Plante into liposomes because doing so not only allows for the protein to obtain native-like conformation, but also has the added benefit of the inherent immunoadjuvant activity of the liposome vesicles. The secondary references further teach that the liposomes may be used with or without a further adjuvant.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references **individually** where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). The prior art, taken as a whole, clearly provides motivation for combining/formulating a known Neisseria protein with a liposome of any origin, including one comprising a bacterial phospholipid. It is noted that the instant disclosure allows for the liposome to be synthesized or extracted from bacterial cells, soybeans or eggs. Phosphatidyl choline, phosphatiddylserine, phosphatidylgycerol, glycerides, steroids, e.g., cholesterol are all suggested.

It is noted that only instant claims 17 and 19 require the additional use of an adjuvant. The secondary references further teach that the liposomes may be used *with or without* a further adjuvant. Wright et al specifically teach that reactivity with native protein was considerably enhanced by incorporation of the adjuvant monophosporyl lipid A into the liposome.

The protein claimed and fragments thereof was very well known at the time the invention was made. Additionally, it was very well known that extensively teach that incorporating isolated, denatured or recombinant *N.meningitidis* proteins into liposomes allows for the proteins to achieve optimal protein folding which allowed for native-like conformation. It is taught that the use of liposomes replaced the use of LPS to promote native-like folding of the protein to an active conformation without the negative toxic effects associated with LPS. One of ordinary skill in the art would have been motivated to incorporate the known NSA protein taught by Plante into liposomes, including those comprising a bacterial phospholipid, because doing so not only allows for the protein to obtain native-like conformation, but also has the added benefit of the inherent immunoadjuvant activity of the liposome vesicles.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645